REMARKS/ARGUMENTS

Claims 119-121 and 123 are pending in this application and are rejected on various grounds. Rejections to these claims are respectfully traversed.

Priority

Based on the rejections presented in the Final Office action, Applicants readdress priority. Applicants submit that they rely on the 'gene amplification' assay (Example 143) for patentable utility of the instantly claimed subject matter. This utility was first disclosed in the U.S. Provisional Patent Application Serial No. 60/141,037, filed June 23, 1999, priority for which has been claimed in this application and relevant pages of which have been submitted to the Examiner with the previous response. Applicants believe that they are at least entitled to an effective filing date of **June 23, 1999** based on the results of the 'gene amplification' assay for the present case.

The Examiner has indicated that the gene amplification assay was not found to be enabling as required by the 35 U.S.C. §112, first paragraph. The Examiner says regarding Sen that "Sen includes no teaching that all aneuploid tissues are cancerous or pre-cancerous, not did the Examiner make any such statement. Rather, both Sen and the Examiner state that cancerous tissues are known to be aneuploid. It is also true that pre-cancerous tissues may be aneuploid. The converse is not true. Aneuploidy is also a feature of damaged tissue, and is commonly found in colon tissues....It does not invariably lead to cancer" (emphasis added). Applicant respectfully disagree with some of the Examiner's statements.

Applicants had asserted patentable utility for the PRO1111 molecule based on the amplification of the gene encoding PRO1111. The gene encoding PRO1111 was amplified approximately 1.05-1.58 ΔCt units in seven lung tumors and 1.05-1.38 ΔCt units in four colon tumors which corresponds to $2^{1.05}$ -$2^{1.58}$- fold amplification in lung and $2^{1.05}$ -$2^{1.38}$- fold amplification in colon tumors respectively, or **2.0705 to 2.99 fold** in seven different lung primary tumors and **2.0705 to 2.603 fold** in four different colon primary tumors. Applicants submit that, one skilled in the art would find it more likely than not that PRO1111 is useful as a diagnostic tool for detecting certain lung or colon tumors.

As the Examiner points out, aneuploidy can be a feature of damaged tissue as well, besides cancerous or pre-cancerous tissue, and may not invariably lead to cancer. However, Applicants submit that the art shows that "epithelial tumors develop through a multistep process driven by genetic instability" in damaged lesions. Applicants provide a reference by Hittelman *et al.* (copy enclosed) to support this view. This reference is merely provided as supportive evidence for an assertion of utility, its consideration is respectfully requested. Hittelman studied damaged or premalignant lesions and suggests that epithelial tumors develop through a multistep process driven by genetic instability (see abstract). Hittelman showed that a subset of the same molecular changes found in associated tumors were also found in premalignant lesions, suggesting that these premalignant lesions might represent precursor lesions for associated tumors, i.e., a manifestation of a multistep tumorigenesis process. (See Hittelman, page 4, last three lines). Applicants submit that there is utility in identifying genetic biomarkers in epithelial tissues at cancer risk (also see Hittelman, abstract, line 4-7). Hittelman adds on page 2, fourth paragraph, line 3 that "it is important to identify individuals at significantly increased cancer risk who might best benefit from different types of intervention."

Taken together, even if the observed PRO1111 gene amplification were due to chromosomal aneuploidy (which Applicants do not contend to), it still supports at least one utility for the PRO1111 gene according to Hittelman, because it helps in identifying individuals at significantly increased cancer risk. Therefore, the art supports at least one utility for the PRO1111 gene, that is, as a genetic biomarker for cancer or precancerous cells. As one skilled in the art would clearly knows, early detection of lung cancer provides information in advance about risk assessment, prognosis and therapy for lung cancer. Accordingly, the encoded polypeptide or antibodies produced thereof find utility as a diagnostic of cancer or individuals at risk of cancer.

Applicants also respectfully remind the Examiner that to overcome the presumption of truth that an assertion of utility by the Applicant enjoys, the Examiner must establish that it is "more likely than not" that one of ordinary skill in the art would doubt the truth of the statement of utility. The above remarks in this rejection by the Examiner are a clear indication that the Examiner applies a standard that might be appropriate, if the issue at hand were the regulatory

approval of a diagnostic assay based on the overexpression of PRO1111 in lung or colon tumor, but is fully inappropriate for determining if the "utility" standard of the Patent Statute is met. The FDA reviewing an application for a new diagnostic assay will indeed ask for actual numerical data, statistical analysis, and other specific information before a diagnostic assay is approved. However, the Patent and Trademark Office is not the FDA, and the standards of patentability are not the same as the standards for market approval. It is well established law that therapeutic utility sufficient under the patent laws is not to be confused with the requirements of the FDA with regard to safety and efficacy of drugs to be marketed in the United States. *Scott v. Finney*, 34 F.3d 1058, 1063, 32 USPQ2d 1115, 1120 (Fed. Cir. 1994). Indeed, in *Nelson v. Bowler*, 626 F.2d 853, 856, 206 USPQ 881, 883 (CCPA 1980), the Federal Circuit found that the identification of a pharmacological activity of a compound provides an "immediate benefit to the public" and satisfies the utility requirement. This logically applies to a diagnostic utility as well. The identification of a diagnostic utility for a compound should suffice to establish an "immediate benefit to the public" and thus to establish patentable utility for PRO1111.

The Examiner further says on page 3, second paragraph of the Final Office Action that "there has been not been "significant difference relative to normal tissue" established for PRO1111 protein, nor is such predictable from a 2-3 fold amplification of the nucleic acid encoding such in a minority of tested samples." Applicants respectfully disagree.

First of all, as evidence that the "increase in DNA" in the gene amplification assay is significant, Applicants submit a Declaration by Dr. Audrey Goddard (copy enclosed herewith). The Declaration by Dr. Audrey Goddard provides a statement by an expert in the relevant art that "fold amplification" values of at least 2-fold are considered significant in the TaqMan™ PCR gene amplification assay. This Declaration is necessary at this time to address the significance of the fold-amplification for the PRO1111 gene. The issue whether the fold increase in the gene amplification assay for the PRO1111 gene was "significant" was not raised in the First Office Action mailed July 1, 2004. Therefore, this declaration addressing "significance" was not presented earlier since the Applicants had no opportunity or reason to address this issue until now. Thus, good and sufficient reasons exist why this Declaration is necessary and was not

earlier presented. Applicants therefore submit that entry of the Goddard Declaration is appropriate at this time and respectfully request that it be considered..

Applicants particularly draw the Examiner's attention to page 3 of the Goddard Declaration which states that:

> It is further my considered scientific opinion that an at least **2-fold increase** in gene copy number in a tumor tissue sample relative to a normal (*i.e.,* non-tumor) sample is significant and useful in that the detected increase in gene copy number in the tumor sample relative to the normal sample serves as a basis for using relative gene copy number as quantitated by the TaqMan PCR technique as a diagnostic marker for the presence or absence of tumor in a tissue sample of unknown pathology. Accordingly, a gene identified as being amplified at least 2-fold by the quantitative TaqMan PCR assay in a tumor sample relative to a normal sample is **useful as a marker for the diagnosis of cancer**, for monitoring cancer development and/or for measuring the efficacy of cancer therapy. (Emphasis added).

Accordingly, the **2.0705 to 2.99 fold** amplification in seven different lung primary tumors and **2.0705 to 2.603 fold** amplification in four different colon primary tumors would be considered significant and credible by one skilled in the art, based upon the facts disclosed in the Goddard Declaration.

The Examiner once again quotes Haynes *et al.,* Pennica *et al.* and Konopka *et al.* to show that "an increase in nucleic acid copy number is not predictive of a similar association for protein." Applicants respectfully disagree for the reasons submitted in the response mailed November 1, 2004.

Briefly, the teachings of Pennica *et al.* and Konopka *et al.* are not directed towards genes in general but to a single gene or genes within a single family and thus, their teachings cannot support a general conclusion regarding correlation between gene amplification and mRNA or protein levels. Further, Applicants submit that the teachings of Haynes *et al.* in fact, meets the "more likely than not standard" and shows that a positive correlation exists between mRNA and protein. Applicants have submitted ample evidence to show that, in general, if a gene is amplified in cancer, it is more likely than not that the encoded protein will also be expressed at an elevated level. First, the articles by Orntoft *et al.*, Hyman *et al.*, and Pollack *et al.* submitted in the response filed November 1, 2004 collectively teach that in general, gene amplification

increases mRNA expression. Orntoft *et al.* studied transcript levels of 5600 genes in malignant bladder cancers, many of which were linked to the gain or loss of chromosomal material, and found that in general (18 of 23 cases) chromosomal areas with more than 2-fold gain of DNA showed a corresponding increase in mRNA transcripts. Hyman *et al.* compared DNA copy numbers and mRNA expression of over 12,000 genes in breast cancer tumors and cell lines, and found that there was evidence of a prominent global influence of copy number changes on gene expression levels. In Pollack *et al.*, the authors profiled DNA copy number alteration across 6,691 mapped human genes in 44 predominantly advanced primary breast tumors and 10 breast cancer cell lines, and found that on average, a 2-fold change in DNA copy number was associated with a corresponding 1.5-fold change in mRNA levels. In summary, the evidence supports the Appellants' position that gene amplification is more likely than not predictive of increased mRNA and polypeptide levels.

Second, the Declaration of Dr. Paul Polakis (submitted in the response filed November 1, 2004), principal investigator of the Tumor Antigen Project of Genentech, Inc., the assignee of the present application, shows that, in general, there is a correlation between mRNA levels and polypeptide levels. Taken together, although there are some examples in the scientific art that do not fit within the central dogma of molecular biology that there is a correlation between DNA, mRNA, and polypeptide levels, these instances are exceptions rather than the rule. In the majority of amplified genes, as exemplified by Orntoft *et al.*, Hyman *et al.*, Pollack *et al.*, the Polakis Declaration and the widespread use of array chips, the teachings in the art overwhelmingly show that gene amplification influences gene expression at the mRNA and protein levels. Therefore, one of skill in the art would reasonably expect in this instance, based on the amplification data for the PRO1111 gene, that the PRO1111 polypeptide is concomitantly overexpressed.

The Examiner further quotes reference Hu *et al.* on page 6 of the Final Office Action and says that "among genes with a 10-fold or more change in expression level, there was a strong and significant correlation between expression level and a published role in the disease." Applicants respectfully disagree.

Contrary to the Examiner's assertion, the cited Hu *et al.* reference does not conclusively establish a *prima facie* case for lack of utility for the PRO1111 molecule. The Hu *et al.* reference is entitled "Analysis of Genomic and Proteomic Data using Advanced Literature Mining." Therefore, as the title itself suggests, the conclusions in this reference are based upon statistical analysis of information obtained from published literature, and not from experimental data. Hu *et al.* performed statistical analysis to provide evidence for a relationship between mRNA expression and biological function of a given molecule (as in disease). The conclusions of Hu *et al.* however, only apply to a specific type of breast tumor (estrogen receptor (ER)-positive breast tumor) and cannot be generalized to breast cancer genes in general, let alone to cancer genes in general. Interestingly, the observed correlation was only found among ER-positive (breast) tumors not ER-negative tumors." (See page 412, left column).

Moreover, the analytical methods utilized by Hu *et al.* have certain statistical drawbacks, as the authors themselves admit. For instance, according to Hu *et al.*, "*different statistical methods* " were applied to "*estimate* the strength of gene-disease relationships and evaluated the results." (See page 406, left column, emphasis added). Using these different statistical methods, Hu *et al.* "[a]ssessed the relative strengths of gene-disease relationships based on the frequency of both co-citation and single citation." (See page 411, left column). As is well known in the art, different statistical methods allow different variables to be manipulated to affect the resulting outcome. In this regard, the authors disclose that, "Initial attempts to search the literature" using the list of genes, gene names, gene symbols, and frequently used synonyms generated by the authors "revealed several sources of false positives and false negatives." (See page 406, right column). The authors add that the false positives caused by "duplicative and unrelated meanings for the term" were "difficult to manage." Therefore, in order to minimize such false positives, Hu *et al.* disclose that these terms "had to be eliminated entirely, thereby reducing the false positive rate but unavoidably under-representing some genes." *Id.* (Emphasis added). Hence, Hu *et al.* had to manipulate certain aspects of the input data, in order to generate, in their opinion, meaningful results. Further, because the frequency of citation for a given molecule and its relationship to disease only reflects the current research interest of a molecule, and not the true biological function of the molecule, as the authors themselves acknowledge, the "[r]elationship

established by frequency of co-citation do not necessarily represent a true biological link." (See page 411, right column). Therefore, based on these findings, the authors add, "[t]his may reflect *a bias in the literature* to study the more prevalent type of tumor in the population. Furthermore, this emphasizes that caution must be taken when interpreting experiments that may contain subpopulations that behave very differently." *Id.* (Emphasis added). In other words, some molecules may have been underrepresented merely because they were less frequently cited or studied in literature compared to other more well-cited or studied genes. Therefore, Hu *et al.*'s conclusions are not based on genes/mRNA *in general.*

Therefore, Applicants submit that, based on the nature of the statistical analysis performed herein, and in particular, based on Hu's analysis of *one* class of genes, namely, the estrogen receptor (ER)-positive breast tumor genes, the conclusions drawn by the Examiner, namely that, "genes displaying a 5-fold change or less (mRNA expression) in tumors compared to normal showed no evidence of a correlation between altered gene expression and a known role in the disease (in general)" is not reliably supported.

Therefore, when the proper legal standard is used, a *prima facie* case of lack of utility has not been met based on the cited references Pennica *et al.,* Haynes *et al.* or Hu *et al.* by the Examiner.

Thus, Applicants have demonstrated utility for the PRO1111 polypeptide and its antibodies based on the gene amplification assay and thus, Applicants request that the Examiner reconsider the priority date for the present application based on the present arguments.

Claim Rejections – 35 U.S.C. §102

1) Claims 119-121 remain rejected under 35 U.S.C. §102(a) or (b) as being anticipated by Jacobs, WO 99/50405 (pub 10/7/1999).

2) Claims 119-121 and 123 remain rejected under 35 U.S.C. §102(e) as being anticipated by Shimkets, U.S. Patent No. 6,689,866 or U.S. Patent Pub US2003/0054514 or U.S. Patent Pub US2003/0003532 (dated 3/8/00).

As discussed above, Applicants are at least entitled to an effective filing date of **June 23, 1999** based on the results of the 'gene amplification' assay for Claims 119-121 and 123,

and this date precedes the publication date for Jacobs and Shimkets. Therefore, neither Jacobs nor Shimkets are prior art. Therefore, these rejections should be withdrawn.

Claim Rejections – 35 U.S.C. §103(a)

1) Claims 119-120 and 123 remain rejected under 35 U.S.C. §103(a) as being obvious over any one loci AI769814, AI435407, AI470931 or T15752 in view of Sibson et al.

2) Claim 121 remains rejected under 35 U.S.C. §103(a) as being obvious over any one loci AI769814, AI435407, AI470931 or T15752 in view of Sibson et al. and further in view of USPN 5,565,332 (Hoogenboom) in the case of Claim 121, or in view of U.S. Patent No. 4,946,778 (Ladner) in the case of Claim 122.

Applicants respectfully remind the Examiner that the instant case is directed to **antibodies**, particularly, to antibodies to the polypeptide of SEQ ID NO: 229, and not to nucleic acids. Applicants note that the polypeptide sequences encoded by AI769814, AI435407, AI470931 or T15752 were not reduced to practice in the cited art nor did the art provide any disclosure whatsoever of the full-length polypeptide encoded by any of these nucleic acid fragments. Hence this rejection directed to the instant antibodies based on nucleic acid ESTs alone is not appropriate and therefore, AI769814, AI435407, AI470931 or T15752 are not prior art.

Since the primary references fall as 103(a) references, and Sibson or Hoogenboom or Ladner do not teach SEQ ID NOs: 229 and 228 of the instant application, this rejection falls and should be withdrawn.

3) Claim 123 remains rejected under 35 U.S.C. §103(a) as being obvious over Jacobs, WO99/50405 (dated pub 10/7/1999).

As discussed above, Applicants are at least entitled to an effective filing date of **June 23, 1999** based on the results of the 'gene amplification' assay for Claims 119-121 and 123, and this date precedes the publication date for Jacobs. Accordingly, this rejection should be withdrawn.

The present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. **08-1641** (referencing Attorney's Docket No. **39780-2730 P1C18**).

Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

Date: November 9, 2005

By:_____
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